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ORIGINAL ARTICLE

Helicobacter pylori Infection in Rural China: Exposure to Domestic Animals During Childhood and Adulthood

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Little is known about the mode of transmission of Helicobacter pylori, one of the most common human bacterial infections. Some domestic animals, including the cat, have been suggested as a reservoir of H. pylori disease, but the data have been inconsistent. This paper evaluates the role of exposure to pets and other domestic animals in the etiology of H. pylori in a rural area of China with a high prevalence of H. pylori infection. In this double-blind, population-based, cross-sectional investigation, interviews were completed with 3288 (1994 seropositive, 1019 seronegative, 275 indeterminate) H. pylori-infected adults enrolled in a randomized intervention trial in Linqu County, Shandong Province, China. We found no evidence to suggest that exposure to pets or other domestic animals during either childhood or adulthood was related to the prevalence of H. pylori infection. In fact, odds ratios (ORs) were reduced for subjects who had kept a cat (OR = 0.7, 95% CI = 0.4–1.0) or any animal (OR = 0.5, 95% CI = 0.3–0.9) in the house as an adult, or a cat as a child (OR = 0.7, 95% CI = 0.5–1.0). ORs were also reduced for all 11 types of animal studied that subjects had kept in their courtyard as an adult. These findings suggest that zoonotic transmission, including that from domestic cats, is an unlikely route of H. pylori infection in this rural Chinese population.

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INTRODUCTION

Helicobacter pylori is one of the most common bacterial infections among humans, but little is known about its mode of transmission. Although the principal reservoir for H. pylori infection appears to be people, it has been isolated from non-human primates (1). Other animals have also been suggested as a reservoir for the disease, including the domestic cat, but the data have been inconsistent (2–4). In 1997–98, a cross-sectional study of 3288 adults aged 35–69 y enrolled in an intervention trial in Linqu County, Shandong Province, China was conducted to assess possible risk factors that may be associated with H. pylori infection. This area of China has a high prevalence of H. pylori among children and adults (5) and one of the highest rates of gastric cancer in the world (6). Although an earlier investigation found that nearly 70% of children aged 5–6 y in this area of rural China were infected with H. pylori (7), follow-up of H. pylori-negative subjects and antibiotic-treated H. pylori-positive subjects participating in the intervention trial suggested that transmission of H. pylori during adulthood may be more common in rural China than previously expected (unpublished data). Therefore, this paper evaluates whether an association exists between H. pylori seropositivity and exposure to pets and other domestic animals during either childhood or adulthood, and whether zoonotic transmission is a likely mode of transmission in this high-risk area of rural China.

MATERIALS AND METHODS

This study is a double-blind, population-based, cross-sectional investigation of 3288 H. pylori- infected and -uninfected adults enrolled in a joint National Cancer Institute (NCI)/Beijing Institute for Cancer Research (BICR) randomized intervention trial to inhibit progression of precancerous gastric lesions in Linqu County, Shandong Province, China. Details of the intervention trial study population and methodology have been presented in detail elsewhere (8). In brief, as part of a previous NCI/BICR study of precancerous gastric lesions, the names of all residents aged 35–64 y were transcribed in 1989 from village lists in 13 villages selected at random from 5 townships. The names of all individuals aged 35–39 y, from the same 13 villages, were added to the study roster in 1994. Chinese health officials visited the 4326 individuals on the roster in 1994, explained the study and obtained written informed consent for their participation in a screening program that included interview, gastroscopy, gastric biopsy and phlebotomy. Of the 4035 participants, 3599 (89%) were eligible to participate in the intervention trial and 3411 (95% of those eligible) were enrolled in September 1995.

Interview and questionnaire

For the cross-sectional study, personal interviews lasting ≈ 15 min were conducted in Chinese in the homes of H. pylori-infected and -uninfected subjects by trained BICR field staff between October 1997 and May 1998. Both the interviewers and interviewees were blinded to the H. pylori serostatus of the study participants. The

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questionnaire was designed to study risk factors for infectious disease in general and H. pylori in particular and to investigate potential modes of transmission. Information was collected on childhood socioeconomic factors, personal hygiene and exposure to food, drinking water, waste water and animals. Questionnaire data were merged with a file containing H. pylori serology test results (used as the measure of H. pylori infection) and pathology data (used to evaluate status of gastric mucosa; biopsy-based confirmation of H. pylori was not performed) obtained from the same population. As a quality control measure, interviews were tape recorded for review by the field supervisor. Informed consent to participate in the study was obtained from each subject prior to interview. The study received clinical exemption from the Office of Management and Budget and was approved by Institutional Review Boards at BICR, Westat, Inc. and NCI.

Blood collection and analysis

In 1994, prior to the start of the intervention trial, a 5-ml blood sample was collected from eligible subjects. Serum was separated and aliquoted in the field, stored immediately at -20°C, and then transferred to a -70°C freezer at BICR. One aliquot of serum (0.5 ml) was tested by one of the authors (L. Z.) for IgG and IgA antibodies to H. pylori (5). H. pylori strains cultured from gastric biopsies of 2 patients in Linqu County were used to provide the antigenic preparation for serology as it had been suggested that assays based on indigenous strains may perform better (9). However, when an H. pylori assay based on pooled antigens from US strains and an assay based on a pool of Chinese strains were subsequently tested using sera from 132 Chinese study subjects with biopsy-proven H. pylori infection, using cutpoints designed to yield equal specificities of 94.9% in an uninfected control population, the sensitivities of the 2 assays were not statistically different (10). Based on data from the pilot village for the intervention trial, the sensitivity and specificity of the 2-strain Chinese assay were 90% and 87%, respectively, compared to the ^{13}C urea breath test. No specific characteristics of the indigenous strains used in the Chinese assay, including cytotoxin-associated protein (cagA) status, were known. All assays were performed on coded samples in duplicate and then repeated. The average of the duplicate values for each of the 2 repeated assays was recorded. Each microtiter plate was read at 414 nm. For stratification in the intervention trial, each subject was considered positive for H. pylori infection if the ELISA absorbance reading for IgG or IgA was ≥ 1.0 on either of the repeated assay values, a cutoff based on examination of the distribution of readings in relation to a group of uninfected persons and reference sera (5). For the present analysis of the cross-sectional data, more stringent definitions of seropositivity and seronegativity were employed, and subjects were categorized as either seropositive, seronegative or indeterminate. A subject was considered seropositive if both IgG optical density readings were ≥ 1.1 and seronegative if both IgG values were ≤ 0.9 and neither IgA value was ≥ 1.0. Otherwise, subjects were categorized as indeterminate. Subjects with one or no IgG values, regardless of their IgA status, were included in the indeterminate category.

Data analysis

The measure of association used in this analysis is the prevalence odds ratio (OR) comparing “definitively” H. pylori seropositive to “definitively” H. pylori seronegative subjects. Because the outcomes were multinomial (i.e. negative, positive and indeterminate) maximum likelihood estimates were computed using polychotomous logistic regression (11). Because H. pylori infection status may be correlated within families and about half of the study subjects came from households with >1 participating member, standard calculations of variances based on the polychotomous logistic model that assume that responses are independent, conditional on covariates, may be misleading in this application. Therefore, to estimate the needed variances and covariances, 100 bootstrap replicates based on resampling families with replacement were used. Age, as a continuous variable, was included in all logistic models to control for potential confounding. Other variables, such as village and village education status, were not found to be significant confounders or effect modifiers, and thus were not included in the logistic regression models. Presented for each variable is the prevalence odds ratio, the 95% confidence interval (CI) computed directly from the polychotomous logistic regression and the bootstrap 95% CI that allows for additional familial correlation.

RESULTS

Interviews were completed with 3288 (96.4%) of the 3411 study subjects enrolled in the intervention trial. Reasons for non-response included death (54 subjects; 1.6%), dropping out of the trial (33 subjects; 1.0%), lost to follow-up (10 subjects; 0.3%) and refusal (26 subjects; 0.8%). The H. pylori serostatus of the participants was positive for 1994 subjects (60.6%), negative for 1019 subjects (31.0%) and indeterminate for 275 (8.4%). H. pylori serostatus by age, gender and gastric pathology is presented in Table I. The percentage of seropositive subjects decreased somewhat with age, ranging from 63% in those aged <40 y to 57% in those aged ≥ 55 y. The percentage of seropositive subjects was higher in females (63%) than males (59%). The percentage of seropositive subjects varied greatly with gastric pathology category. Subjects with normal gastric mucosa or superficial gastritis had the lowest prevalence of H. pylori infection (28%); intermediate levels (46%) were seen for subjects with mild chronic atrophic gastritis (CAG); and higher levels (67–77%) were seen for subjects with moderate or severe CAG, intestinal metaplasia and dysplasia. The highest prevalence of infection was seen for subjects with cancer (80%), although this figure was based on only 5 subjects. The determination of H. pylori status using serology, which indicates past and present infection with H. pylori, instead of biopsy-based methods, which indicate only current infection, may account for the unexpectedly high prevalence in this study of H. pylori associated with severe gastric pathology thought to be inhospitable to the H. pylori organism. As expected, median age also increased with extent of gastric pathology, ranging from 41 y for subjects with normal gastric mucosa or superficial gastritis, to 43 y for CAG (mild and severe), 46 y for intestinal metaplasia (deep) and 49 y for dysplasia. There was also significant variation in H. pylori serostaus by village ($\chi^2 = 120.76$, d.f. $= 12$, $p < 0.001$), ranging from 47% to 76%. Annual family income ranged from 40 to 60,000 yuan (median 4000 yuan; $\approx$ US\$500), but there was no association between income level and prevalence of H. pylori infection (data not shown).

Presented in Table II are ORs for the association between the prevalence of H. pylori infection and exposure to pets and other domestic animals during adulthood. Only 7.1% of seropositive subjects and 4.8% of seronegative subjects reported keeping any animal in the house as an adult (OR = 0.7, 95% CI = 0.5–1.0). The OR was significantly reduced for keeping only 1 animal in the house as an adult (OR = 0.5, 95% CI = 0.3–0.9), but there was no correlation between risk and the number of animals kept in the house. Although the following results are not statistically significant, ORs were reduced for keeping cats (OR = 0.6, 95% CI = 0.3–1.1) or rabbits (OR = 0.7, 95% CI = 0.4–1.1), but not dogs (OR = 1.2, CI = 0.3–4.5). There was also a modest reduction in the OR associated with keeping any animal in the subject's courtyard as an adult (OR = 0.8, 95% CI = 0.5–1.2). ORs were reduced for all 11 types of animals studied that were kept in the courtyard, including cats (OR = 0.7), dogs (OR = 0.9), chickens (OR = 0.8), sheep (OR = 0.3), cows (OR = 0.6) and pigs (OR = 0.8). The OR was also not elevated for subjects whose job involved working with animals (OR = 0.5, 95% CI = 0.2–1.2).

The association between the prevalence of H. pylori infection and exposure to pets and other domestic animals during childhood is presented in Table III. Overall, there were no associations between H. pylori infection and keeping any animals in the house or the number of animals kept in the house when the subject was 10 y old. However, the ORs associated with keeping cats (OR = 0.7, 95% CI = 0.5–1.0) or dogs (OR = 0.5, 95% CI = 0.3–1.0) in the house when the subject was 10 y old were reduced.

DISCUSSION

This cross-sectional study found no evidence to suggest that exposure to pets or other domestic animals during either childhood or adulthood was related to the prevalence of H. pylori infection in this area of rural China. In fact, ORs were reduced for adults who kept cats or any animal in the house. Similar reductions in ORs were seen for the presence of cats in the household when the subject was 10 y old. ORs were also reduced for all types of animals that were kept in the study subject's courtyard, including sheep (although based on very small numbers) and cats and the most common large animals kept in this rural area, namely pigs, goats and cows. No information was sought on childhood exposure to sheep or other farmyard animals.

These data are consistent with the majority of epidemiologic studies which suggest that ownership of a pet as an adult or child is not associated with a higher prevalence of H. pylori infection (12–21). In fact, 2 studies in the US found pet owners to have significantly lower rates of H. pylori infection (14, 20). It is possible that lower rates in pet owners may be due to confounding by social class. However, 1 large population-based study in Canada (21) that adjusted for social class found no association between pet ownership and a history of peptic ulcer disease (21), and in our study population there was no association between annual family income and prevalence of H. pylori infection. The OR in our study was not elevated for subjects who had a job working with animals, in agreement with studies

Table I. *H. Pylori serostatus of cases and controls by age, gender and gastric pathology* [a]

	H. pylori-positive		H. pylori-negative		Indeterminate	
Factors	*n* = 1994	Row% = 60.6	*n* = 1019	Row% = 31.0	*n* = 275	Row% = 8.4
Age (years)						
<40	484	(63)	219	(28)	67	(9)
40–44	530	(62.5)	250	(29)	68	(8)
45–54	537	(60)	290	(32)	66	(7)
55–59	170	(57)	102	(34)	27	(9)
>60	273	(57)	158	(33)	47	(10)
Gender						
Male	978	(59)	536	(32)	155	(9)
Female	1016	(63)	483	(30)	120	(7)
Grouped gastric pathology categories						
Normal, SG	21	(28)	47	(64)	6	(8)
Mild CAG	546	(46)	523	(45)	104	(9)
Moderate, severe CAG	188	(77)	37	(15)	19	(8)
IM superficial	183	(67)	71	(26)	21	(8)
IM deep	656	(71)	190	(21)	78	(8)
Dysplasia	298	(68)	105	(24)	34	(8)
Cancer	4	(80)	1	(20)	0	–
Missing	98	(63)	45	(29)	13	(8)

[a] SG = superficial gastritis; CAG = chronic atrophic gastritis; IM = intestinal metaplasia.

Table II. *Association between prevalence of H. pylori infection and exposure to domestic animals during adulthood*

Animal variables	Positive	Negative	OR [a]	95% CI	95% CI [b]
Number of animals kept in the house					
No animals	1897	947	1.0	–	–
Some animals	96	72	0.7	0.5–0.9	0.5–1.0
1	38	37	0.5	0.3–0.8	0.3–0.9
2–4	22	13	0.9	0.4–1.7	0.4–1.7
>4	33	19	0.9	0.5–1.6	0.5–1.7
Types of animals kept in the house					
No animals	1897	947	1.0	–	–
Cats	33	27	0.6	0.4–1.0	0.3–1.1
Dogs	7	3	1.2	0.3–4.5	NA [c]
Rabbits	47	34	0.7	0.4–1.1	0.4–1.1
Types of animals kept in the courtyard					
No animals	62	27	1.0	–	–
Some animals	1932	992	0.8	0.5–1.3	0.5–1.2
Cats	26	15	0.7	0.3–1.5	0.3–1.6
Chickens	1617	856	0.8	0.5–1.2	0.4–1.4
Cows	307	189	0.6	0.4–1.1	0.4–1.1
Dogs	365	164	0.9	0.6–1.5	0.6–1.5
Donkeys	68	40	0.7	0.4–1.3	0.4–1.3
Ducks	956	502	0.8	0.5–1.2	0.5–1.3
Geese	253	145	0.7	0.4–1.2	0.4–1.2
Goats	488	242	0.8	0.5–1.4	0.5–1.4
Pigs	1469	759	0.8	0.5–1.2	0.5–1.2
Rabbits	346	180	0.8	0.5–1.3	0.5–1.4
Sheep	2	3	0.3	0.04–1.7	NA [c]
Had job working with animals					
No	1981	1006	1.0	–	–
Yes	9	11	0.5	0.2–1.1	0.2–1.2

[a] Adjustment for age in a polychotomous logistic model.
[b] Calculated using bootstrap technique.
[c] Not available because the sample size was too small.

conducted in Australia and Germany that reported no association with occupational handling of animals (12, 15).

Although 2 studies found no significant association between H. pylori infection and having a cat during childhood (19, 22), a study in Germany by Rothenbacher et al. (15) found that adults who owned a cat as a child had a significantly higher prevalence of H. pylori (45% vs. 31%). The experimental data on cats are also inconsistent. The isolation of H. pylori from laboratory domestic cats raised the possibility that it could be transmitted from cats to humans via saliva, vomit or feces (3, 23, 24). However, no evidence of H. pylori infection was found in an investigation of stray cats or healthy pet cats (4, 25, 26). Instead, another Helicobacter species, H. helmanni, was considered responsible for the chronic gastritis seen in these cats (4, 25, 26).

There have been no reports of the presence of H. pylori in other common small animals, such as dogs, chickens and rabbits (27, 28). However, the possibility that large animals may serve as a reservoir for H. pylori has received recent attention. Exposure to sheep was implicated in 2 epidemiologic studies (29, 30). In a study of children from the Colombian Andes, Goodman et al. (29) reported that children who "played with sheep" had a higher risk of H. pylori infection (OR = 4.5). A study by Dore et al. (30) revealed that the prevalence of H. pylori was significantly higher among Sardinian shepherds occupationally exposed to sheep than among their non-exposed family members or among Sardinian blood donors. In addition, in Sardinia, 32/32 sheep were seropositive for H. pylori, H. pylori DNA was detected in mucosal strips from the stomach of 3/10 sheep or lambs and H. pylori DNA was present in raw sheep milk (30, 31). In our study, there were too few exposures to sheep to draw conclusions, but there was no evidence of increased risk with exposure to other large animals, such as goats, donkeys, pigs or cows.

The presence of H. pylori in the gastric mucosa of freshly slaughtered calves and pigs in Italy was determined by morphological and histochemical techniques (27). In addition, H. pylori-specific DNA was detected in cow feces in Japan, although its viability was not confirmed (32). H. pylori, however, was not isolated from any of the mucosal specimens collected from the stomachs of 105 cattle from Texas abattoirs (33). Even though the monogastric pig stomach has anatomical and physiologic similarities with the human and non-human primate stomachs (2), evidence that pigs are a reservoir for H. pylori is not convincing.

Table III. *Association between prevalence of H. pylori infection and exposure to domestic animals during childhood*

Animal variables	Positive	Negative	OR [a]	95% CI	95% CI [b]
Number of animals kept in the house at age 10 y					
No animals	1677	853	1.0	–	–
Some animals	312	159	1.0	0.8–1.2	0.8–1.2
1	71	49	0.7	0.5–1.0	0.5–1.1
2–4	97	43	1.1	0.8–1.6	0.7–1.6
>4	131	56	1.1	0.8–1.6	0.8–1.5
Types of animals kept in the house at age 10 y					
No animals	1677	853	1.0	–	–
Cats	70	52	0.7	0.5–1.0	0.5–1.0
Dogs	18	17	1.5	0.3–1.0	0.3–1.0
Rabbits	76	59	1.1	0.9–1.5	0.9–1.4

[a] Adjusted for age in a polychotomous logistic model.
[b] Calculated using bootstrap technique.

The strengths of this cross-sectional investigation are that the data are population-based and were collected in a manner that minimized the risk of bias. Specifically, non-response bias, selection bias, recall bias and information bias were not of major concern because participation rates were high (> 96%); H. pylori status was determined scientifically based on the ELISA optical density test and utilized an indeterminate zone (± 10% of the cutoff value of 1.0); study investigators, interviewers and interviewees were blinded to the H. pylori serostatus of study subjects; the same structured questionnaire was administered to all study subjects in person by trained interviewers; and bootstrap confidence intervals were calculated to avoid underestimation of the standard errors due to possible intrafamilial correlations. Although there may be some degree of misclassification or inaccuracies in the data acquisition, because of the reasons stated above, inaccuracies are not likely to differ systematically according to H. pylori serostatus.

There are, however, several limitations of this study. Similar to all cross-sectional studies, the outcome and exposure were assessed simultaneously, making it difficult to separate cause and effect and to determine temporal relationships; the outcome was measured as prevalence rather than incidence of disease and thus reflects H. pylori infections that could have occurred from early childhood to several weeks before the blood sample was drawn; a lack of heterogeneity in this rural Chinese population may have limited the ability to detect differences between H. pylori-positive and -negative subjects; and recall of information from childhood may have been difficult and inaccurate. It is also possible that almost everyone was exposed to the H. pylori organism during childhood and it was differences in host factors and host susceptibility that determined who became clinically infected.

In summary, our findings suggest that zoonotic transmission, including that from domestic cats, is an unlikely route of H. pylori infection in this rural Chinese population. Further investigation of a possible association between H. pylori and sheep in areas where these exposures are common may be warranted in light of the intriguing experimental and epidemiologic findings.

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